REMARKS

Status of the Claims

Claims 1-25 are pending in the application. Claims 13-15 and 20-25 have been withdrawn as drawn to a non-elected invention. Claims 4, 5, 7, 11, 12, 18, and 19 have been withdrawn as being drawn to a non-elected species. Claims 1-3, 6, 8-10, 16, and 17 are currently under examination.

Claim Amendments

Claim 1 has been amended to recite the full name of PLK4, to clarify that the PLK is PLK4, and to clarify that a test agent is identified as a candidate beta catenin pathway modulating agent by determining the activity or expression of the PLK4 polypeptide or nucleic acid in the assay system in the presence or absence of the test agent. Support for the amendment is found throughout the specification, and particularly at, for example paragraphs [0005], [0009], [0014], [0070], an [0077 – 0079].

Claims 2 and 8 have been amended to recite that the PLK is PLK4. Support for the amendment is found throughout the specification, and particularly at, for example paragraphs [0005] and [0014].

Claim 10 has been amended to recite the full name for PMO. Support for the amendment is found at paragraph [0054].

Claim 16 has been amended to clarify that the second assay is capable of detecting a change in the beta catenin pathway, that confirmation of the test agent as a candidate beta catenin pathway modulating agent is achieved by measuring the beta catenin pathway in the presence or absence of the test agent, and that the PLK is PLK4. Support for the amendment is found throughout the specification, and particularly at, for example paragraphs [0005], [0009], [0014], [0070], an [0077 – 0079].

Claim 17 has been amended merely to provide proper antecedent basis.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections.

Additionally, these amendments are not an admission regarding the patentability of subject matter of the amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application.

35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-3, 6, 8-10, 16, and 17 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement because the claim(s) contains subject matter that was not described in the specification in such a way so as to enable one skilled in the art to which it pertains, or with which it is most closely connected, to make and/or use the invention. The Applicants respectfully traverse these rejections.

The Office alleged that the identification of Drosophila POLO protein as being any of: members of the Wg pathway, components of apoptotic related pathways, components of cell cycle related pathways, or cell adhesion related proteins and the subsequent identification of PLK4 as a human homolog of Drosphila POLO, along with the demonstration that RNAi of PLK4 decreases proliferation in HT29 and SW480 cells is insufficient to establish a nexus between PLK4 or any PLK and the beta-catenin pathway. Therefore, the Examiner concluded that the claims are not enabled because one skilled in the art could not predictably identify a beta catenin pathway modulating agent using the claimed methods.

The Office further alleged that the claims are broadly drawn to assay systems comprising any PLK nucleic acid and that it is clear from the prior art that each PLK is structurally and functionally distinct and play different roles in cell growth such that the measured test-agent biased activity of the claimed assay using one PLK could not reasonably be extrapolated to the measured results of using a different PLK.

Given that the specification (allegedly) exemplifies only a single PLK, fails to provide a nexus between the beta catenin pathway and any PLK, the art teaches that each PLK is structurally and functionally different (including its

effects on cell proliferation), and that the substrates of PLK4 are unknown, the Office stated that a high amount of experimentation would be required to determine which PLK nucleic acid in which assay system and what test-agent biased activity would be required to predictably identify a beta catenin pathway modulating agent. Thus, the Office concluded that the claims are not enabled because it would require undue experimentation to practice the claimed invention.

The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the application coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Thus, under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention.

Contrary to the Office's allegation, the specification clearly teaches one skilled in the art how to make and use the claimed assay for identifying a candidate beta catenin pathway modulating agent. First, the specification describes the function and structure of the PLK4 polypeptide and further provides exemplary PLK4 polypeptide and nucleic acid sequences that can be used in the screening assays at paragraphs [0005] and [0014]. In addition, the specification clearly provides numerous examples of assays using the described PLK4 polypeptides and nucleic acids that can be employed to identify a candidate beta catenin pathway modulating agent. (Specification at paragraphs [0060] – [0096]. Furthermore, the specification provides numerous examples of assays that can be used to confirm that the identified agent is a beta catenin pathway modulating agent. (Specification at paragraphs [0089] – [0096] Applicant submits that performing the assays described in the specification using the disclosed PLK4 nucleic acids is within the skill of the ordinary artisan.

The Office alleged that the claimed assays are not enabled because there is no established nexus between PLK4 and the beta catenin pathway. Contrary to the Office's contention, the specification provides data linking PLK4 with the

beta catenin pathway. Initially, the specification teaches that the Wnt/beta-catenin pathway is often mutated in human cancers, most notably colorectal cancer, as stated at paragraph [004] on page 1. The mutations in this pathway that contribute to cancer are mutations that cause increased signaling through the pathway, i.e. are activating mutations. Consequently, the Drosophila genetic screen was designed to identify targets that, when inhibited or blocked, cause decreased signaling of the Wnt/beta-catenin pathway.

In Drosophila, the ortholog of the Wnt gene is called Wingless (abbreviated Wg), and the fly ortholog of beta-catenin is called armadillo (abbreviated arm). (Specification at paragraph [0002]. The Drosophila genetic screens were set up to allow the identification of drug targets, which when inhibited or blocked, would decrease signaling through the Wg/armadillo pathway, in keeping with the desired effect in humans to treat tumors. Specifically, flies were genetically engineered with transgenes to express activating mutations in the Wg/armadillo pathway. Several different engineered transgenes were used, and each transgene generated different and specific phenotypes in the fly, depending on exactly where and when the pathway is activated. This reflects the multifunctional nature of this pathway (it does different things in different places). The different transgenes each misexpressed an activated form of the fly beta-catenin homolog armadillo (either arm(S56F) or arm(delta9) mutations) in different times and different tissues, e.g. (a) at an early stage in development of the fly eye tissue hyperactivation of the Wg pathway causes overproliferation of eye tissue cells (i.e. an enlarged eye), or (b) at a late state in development of the fly eye hyperactivation of the Wg pathway causes apoptosis (i.e. necrosis of part of the fly eye), or (c) when hyperactivation of the Wg pathway is caused in ectopic tissue of the fly wing the result is ectopic bristles and veins (where normally there are not bristles or veins). **Three different screens with three different transgenes were used to build redundancy in the screen <u>as an aide to identify components that were bona fide modifiers of the Wg pathway itself, and not other pathways</u>.** Specifically a bona fide modulator of the Wg pathway would be expected to function as a

modulator of all three of these transgenes. Whereas, for example, a gene specifically involved in apoptosis might only modulate the transgene in screen (b) above. Similarly a gene specifically in involved in cell division might only modulate the transgene in screen (a) above, and a gene specifically involved in cell fate might only modulate the transgene in screen (c) above.

In this case, Applicants used the described Drosophila genetic modifier screen to identify a "suppressor" mutation in order to identify genes that are possible anticancer drug targets. Given that loss-of-function mutations in "suppressor" genes result in reduced signaling through the Wg pathway (i.e the suppressor mutations suppress the abnormal phenotype caused by the activating mutation in armadillo), they are genetic surrogates for a drug that inhibits the protein product of that gene. Applicants identified POLO as a bonafide suppressor of the Wg/armadillo pathway in Drosophila through the use of all three genetic screens. The human ortholog of POLO is PLK4, which shares substantial amino acid identity (56%) with POLO.

Human homologs of the Drosophila POLO gene (PLK4) are expected to be potential anticancer drug targets since inhibition of human POLO homologs are expected to cause decreased activity of the Wnt/beta-catenin pathway in humans. Indeed, Applicants validated the results of the Drosophila genetic screen using an inhibitor of PLK4 expression in several functional assays performed using various human tumor cells. Specifically, Applicants showed that:

(a) Inhibition of human PLK4 via RNAi causes decreased proliferation in various human tumor cell lines, including LoVo and HT29 colon cancer cells, PC3 prostate cancer cells, and SW480 colon cancer cells. Specification at paragraph [0125].

(b) Inhibition of human PLK4 via RNAi causes intermediate or late stage apoptosis in human tumor cell lines, including A549 lung cancer cells and PC3 prostate cancer cells. Specification at paragraph [0126].

(c) Inhibition of human PLK4 via RNAi results in a DECREASE in signaling of the Wnt/beta-catenin pathway in human LXI lung cancer cells, SW480 colon cancer cells, and LoVo colon cancer cells as demonstrated using a reporter gene that directly measures signaling of this pathway (TCF transcription factor). Specification at paragraph [0127].

(d) In contrast, overexpression of human PLK4 results in an INCREASE in signaling in the Wnt/beta-catenin pathway in human PC3 prostate cancer cells as demonstrated using a reporter gene that directly measures signaling of this pathway (TCF transcription factor). Specification at paragraph [0127].

(e) Overexpression of PLK4 also causes an increase in the expression of AP1 transcription factor. Specification at paragraph [0128].

(f) The human PLK4 gene is overexpressed in many human tumor types, including breast, colon, head and neck, kidney, liver, lung, lymphoma, prostate, ovarian, pancreatic, skin, stomach, testis, thyroid, and uterine cancers.

To summarize, the results of (c) and (d) above demonstrate that the human PLK4 gene modulates the activity of the Wnt/beta-catenin pathway, in keeping with the results from the Drosophila genetic screen. Results (a), (b), and (e) demonstrate that modulation of PLK4 expression affects cell proliferation and apoptosis in various human tumor cells. Result (f) demonstrates that PLK4 over-expression is associated with various cancers.

Applicants submit that the specification clearly establishes the connection between PLK4 and the beta catenin pathway via the Drosophila genetic screen. Further, the connection between PLK4 and the beta catenin pathway has been

confirmed using reporter gene assays in human cells which show that inhibition of PLK4 expression results in decreased signaling through the beta catenin pathway and increased PLK4 expression results in increased signaling through the beta catenin pathway. In view of the established connection between PLK4 and the beta catenin pathway, and in view of the additional teachings discussed above, Applicants submit that the claimed methods are fully enabled. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 6, 8-10, 16, and 17 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Rejection of Claims Under 35 U.S.C. § 102

Claims 1, 2, 6, 8, 9, 16, and 17 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Spankuch-Schmitt et al., Oncogene, 2002, 21:3162-3171 ("Spankuch-Schmitt"). Applicants respectfully traverse the rejections.

The Office alleged that the claims were anticipated by the teachings of Spankuch-Schmitt which discloses a method comprising: (a) providing a cell culture assay system expressing PLK1 nucleic acid; (b) contacting the assay system with a PLK1 antisense oligomer (test agent) or control; and (c) detecting cell proliferation effects of the test agent or control agent, wherein PLK1 antisense inhibited cell proliferation compared to control. The Office further alleged that Spankuch-Schmitt teaches conducting this assay in three cell culture systems; thus, it teaches conducting the additional steps of providing a second assay system in a different cell culture.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (All elements of the claimed invention must be contained in a single prior art disclosure and must be arranged in the prior art disclosure as in

the claimed invention); M.P.E.P § 2131. The identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir.1990); M.P.E.P. § 2131.

Applicants submit that Spankuch-Schmitt does not teach all of the elements of the presently claimed methods. The claims, as amended, recite a method of identifying a candidate beta catenin pathway modulating agent using an assay system comprising PLK4, which method includes the step of determining the activity or expression of the PLK4 polypeptide or nucleic acid in the assay system in the presence or absence of a test agent. The studies performed by Spankuch-Schmitt are limited to determining the effect of PLK1 antisense on the proliferation of various cells. In view of the fact that Spankuch-Schmitt provides no teaching whatsoever with respect to PLK4, it fails to teach the claimed invention which requires, *inter alia*, providing an assay system capable of detecting PLK4 expression or activity and measuring the expression or activity of PLK4 in the presence or absence of a test agent.

Applicants submit that the Spankuch-Schmitt does not anticipate the present claims because it fails to teach each and every step of the claimed methods. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 USC § 102 (b).

CONCLUSION

In view of the foregoing, the applicants respectfully request reconsideration of the pending claims. If it is believed that such contact would expedite prosecution of the present patent application, the Patent Office is urged to contact the undersigned.

Respectfully submitted,

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